

EDITORIAL

Hypothesis: SARS-CoV-2 transmission is predominated by the short-range airborne route and exacerbated by poor ventilation

1 | INTRODUCTION

It is currently unclear whether a predominant route exists for the transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the pathogen responsible for the coronavirus disease 2019 (COVID-19) pandemic. Following the first reported case of COVID-19 more than 1 year ago in Wuhan, China, more than 100 million people have been infected globally as of early February 2021, and different intervention strategies have been adopted by different countries. A "just-in-case" intervention approach is too extreme, resulting in significant economical and societal losses, while an inadequate approach results in significant infection rates. An adequate intervention strategy demands knowledge of the predominant transmission route(s) of SARS-CoV-2.

It is generally difficult to identify the transmission routes of respiratory infections. Here, we use airborne or (aerosol) inhalation transmission as an example to demonstrate these difficulties. Airborne transmission of SARS-CoV-2 "in specific settings, particularly in indoor, crowded, and inadequately ventilated spaces, where infected person(s) spend long periods of time with others, such as restaurants, choir practices, fitness classes, nightclubs, offices, and/or places of worship" has been acknowledged by the World Health Organization since October 2020.¹ Airborne transmission² refers to the inhalation of air-suspended virus-laden respiratory aerosols by a susceptible person, resulting in infection. These aerosols were previously exhaled by an infected person. Aerosol inhalation can occur over both short and long distances. This definition suggests the need for the following three criteria to be fulfilled to demonstrate airborne transmission.

- An infected individual (with or without subsequent clinical disease) releases sufficient number of viable virus-containing aerosols in the expired air and
- The expired jet and/or the air in the space are not sufficiently diluted; and a sufficient number of virus in aerosols are still infectious, and the virus-containing aerosols can remain suspended in air long enough to be transported to a susceptible person such that
- A susceptible person inhales a sufficient number of aerosols (viable virus) to produce infection,¹⁵ with or without subsequent clinical disease.

These three criteria for demonstrating airborne transmission of any respiratory infection due to expired aerosols, with respect to release, transport/dilution, inhalation, and subsequent infection, are similar to postulates 1–4 proposed by Gwaltney and Hendley.³ However, they are difficult to assess, except in animal studies or human challenge studies, in which it is also difficult to separate inhalation exposure from droplet spray and short-range airborne route. A positive demonstration of these criteria in animal studies may not directly translate to humans, while human challenges are difficult to perform due to ethical considerations. In outbreaks with observed infections, direct evidence of these three criteria mostly disappears after the outbreak has been identified. For SARS-CoV-2, the fulfillment of each individual criteria has been demonstrated in separate studies showing SARS-CoV-2 release by COVID-19 patients,⁴ the presence of viable SARS-CoV-2 particles in the air within a room,⁵ the infection of patrons in a restaurant who sat 4.5 m from the index case without any close contact, and fomite transmission (unpublished). However, no study has provided evidence that satisfies all of the three criteria. The same statement can be made for large-droplet transmission and fomite transmission. In practice, evidentiary support for long-range airborne transmission may be indicated by the fulfillment of any one of the following conditions.⁶

- An outbreak occurred that could be directly attributed to the lack of ventilation air introduction into, and circulation within, an enclosed space.
- The incidence of infection in susceptible hosts was inversely associated with the ventilation rate per person.
- A disease outbreak occurred in an enclosed space, most likely due to air transport of infectious droplet nuclei over a distance greater than 2 m.

Some studies have presented evidence that satisfies these less-stringent criteria for SARS-CoV-2 transmission,⁷ suggesting that airborne transmission of SARS-CoV-2 is likely.

Here, I propose a different approach to demonstrating that SARS-CoV-2 transmission is likely predominated by the short-range airborne route and that long-range airborne transmission is only opportunistic, that is, when ventilation is insufficient.

2 | MAJOR OBSERVED PHENOMENA IN SARS-CoV-2 TRANSMISSION

Einstein's model or the process of epistemology⁸ was used here to develop a theory to explain SARS-CoV-2 transmission. This thought process involves the analysis of observations or experiences. The examination of these observations enables the development of a theory, axiom, or hypothesis, from which we can deduce consequences or predictions that can then be used to explain individual observations or predict new trends. Note that the obtained theory remains as a hypothesis, as "it is even impossible *in principle* to consider a theory 'proven' once and for all, since this would entail subjecting it to an infinity of tests by observation, and not just now but for all future times" (Holton,⁸ page 321).

Summarizing the major phenomena or observations in SARS-CoV-2 transmission can be difficult and subjective. Nevertheless, the following phenomena (O1-O4) may be considered the most representative, based on the increasing amount of scientific literature and infection data. Close-contact transmission appears to dominate in the pandemic (O1). The predominance of close-contact transmission may explain why social distancing measures have been successful. The exact route involved in close-contact transmission cannot be inferred from O1 alone, as we cannot distinguish between large droplets, short-range airborne routes, and short-range surface-touch routes from these data. Most SARS-CoV-2 infections occur indoors (O2).^{9,10} This indoor phenomenon is related to the observation that outdoor transmission is less common or even rare (O3).^{9,10} Neyman and Dalsey¹¹ found no evidence for increased outdoor spread due to Black Lives Matter protests. However, if close-contact transmission dominates, the question remains why close-contact transmission differs in indoor and outdoor settings. The fact that

close contact in outdoor settings has not led to a significant increase in the number of infections, particularly at the initial stage of the pandemic when masks were not worn,¹⁰ reveals that certain characteristics of outdoor locations minimize the infection risk. This will be examined in detail in a later section. Additionally, transmission over long distances within a room has only been reported at some super-spreading events (O4). To the best of my knowledge, the majority of studies have shown that long-range airborne transmission occurs when ventilation is insufficient. Phenomena O1-O4 are sufficient to derive a simple hypothesis as shown in Figure 1.

3 | NEITHER SURFACE-TOUCH NOR LARGE-DROPLET ROUTES OR THEIR COMBINATIONS CAN EXPLAIN THE MAJOR OBSERVED PHENOMENA, O1-O4

Various combinations of the different transmission routes can be tested to explain the aforementioned phenomena. For example, we may first assume that the large-droplet route is responsible for the observed predominance of close-contact transmission (O1), while the airborne route is responsible for long-range infection events (O4), and other routes may exist in a non-predominant manner. This explanation seems to have been partly, although not explicitly, adopted by most health authorities.^{1,13} Can this assumed predominant combination of routes explain O2 and O3? Large-droplet transmission, by its nature, is driven by the initial momentum of the expired droplets ($\geq 50 \mu\text{m}$). These large droplets also tend to fall within a threshold distance, and do not follow the air flow, but they can also deposit on surfaces in their path, for example, the mucus membranes of those in front of the infected individual. The trajectories of these

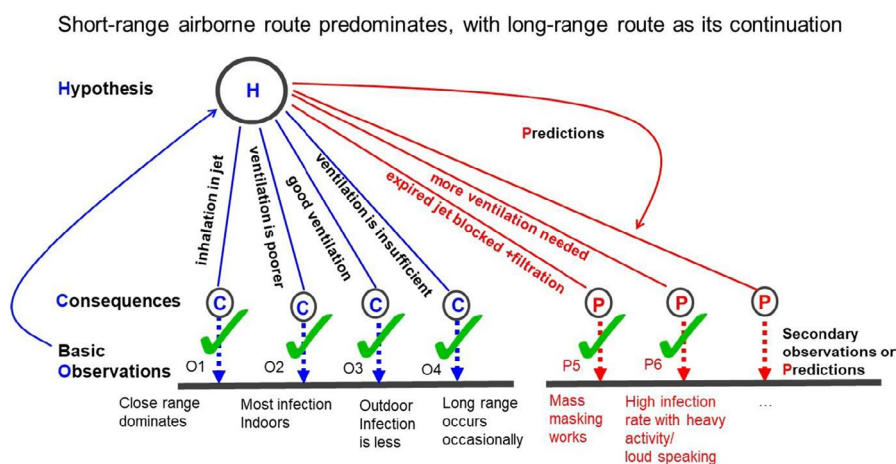


FIGURE 1 The first four basic observed infection patterns in the COVID-19 pandemic (O1-O4) lead to the hypothesis (represented by the top off-centre circle) that the short-range airborne route is predominant, with long-range transmission as its continuation. Consequences are deduced from the hypothesis to explain each of the four basic observations (O1-O4). This hypothesis can also be used to deduce at least two predictions to explain phenomena P5 and P6. Modified from Li et al.¹² The green tick sign means that the specific observation can be explained by the hypothesis. Readers are invited to identify other major phenomena of SARS-CoV-2 transmission or use the hypothesis to predict other trends in the pandemic, to verify or reject our theory. This is shown by an empty "secondary observations or predictions" in the figure. This figure is drawn following a similar thinking process model of Einstein⁸

large droplets over a short distance should not significantly differ between indoor and outdoor settings when the surrounding airflow is weak. Thus, the rare occurrence of outdoor transmission (O3) cannot be explained. Hence, large droplets are not supported as the predominant transmission route. A recent mechanistic study¹⁴ also revealed that exposure to large droplets is insignificant, but short-range airborne exposure dominates.

There is also the possibility of predominant transmission via short-range surface-touch and opportunistic long-range fomite routes. The immediate surfaces of susceptible individuals, such as facial areas and clothing, can be recipients of large droplets exhaled by a nearby source patient. Humans also tend to frequently touch their own surfaces, which may lead to self-inoculation. This combination of surface-touch routes may explain O1 and O4, but it cannot explain the significant difference observed between indoor and outdoor infection risks when people are in close contact (O2 and O3). Our analyses cannot refute the existence of large-droplet and fomite routes. Rather, these two routes are also assumed to occur opportunistically and are not likely to be predominant as they could not explain the major observed phenomena (O1–O4) in SARS-CoV-2 transmission.

4 | SARS-CoV-2 IS LIKELY TRANSMITTED PREDOMINANTLY VIA THE SHORT-RANGE AIRBORNE ROUTE, WITH LONG-RANGE AIRBORNE TRANSMISSION AS ITS CONTINUATION

Is there a single transmission route or a group of transmission routes that can explain all six observed phenomena?

Let us examine how an ideal expired jet works. As a jet develops, its momentum conserves, while its flow rate increases due to entrainment, which leads to a reduction in air speed. Based on simple jet dilution theory, we find that at a distance of 75 times the mouth diameter (ie, 1.6 m if the mouth diameter is 20 mm), air in the jet consists of one portion of air from the mouth and 23 portions from the surrounding air, due to entrainment. Thus, the jet is diluted 24-fold at 1.6 m. The concentration of expired aerosols in the jet air is a mixture of those in the expired airflow at the origin and those in the entrained surrounding air. In outdoor settings, the surrounding air is expected to be “clean.” However, in a room, the concentration of expired aerosols in the air is determined by ventilation, deactivation, and deposition, in addition to the source strength. If ventilation is insufficient, air in the room can have a significant level of “contamination,” and 23 portions of this air cannot dilute the expired jet at 1.6 m, as it does in outdoor settings. At steady state and fully mixed conditions, a simple calculation shows that at rest, a ventilation rate less than 3 L/s per person would significantly increase the infection risk, while a ventilation rate greater than 10 L/s per person would produce conditions that mimic outdoor settings.

At least one other factor makes short-range airborne transmission of SARS-CoV-2 predominant. The number of droplets involved in short-range airborne transmission is much greater than that

involved in long-range transmission. Only those droplet nuclei with a diameter $\leq 5 \mu\text{m}$ (ie, a diameter likely $\leq 15 \mu\text{m}$ at the origin of expiration) can remain suspended in room air. Therefore, droplets with a diameter between approximately 15 and 50 μm at the origin of expiration settle out from room air after they are dispersed out of the expired jet and are not available for inhalation.

The above jet dilution analysis strongly suggests that ventilation affects the infection risk in both long- and short-range airborne exposure events. Poor ventilation increases short-range airborne transmission. Close-range concentration profiles are similar in indoor settings with sufficient ventilation rates ($\geq 10 \text{ L/s}$ per person for resting conditions) and in outdoor settings with an infinite ventilation rate (not shown). A sufficient ventilation rate can reduce the close-range infection risk in indoor settings to a level similar to that in outdoor settings, if reasonable inter-personal distances are maintained. Further analysis of close-range infection risk will be presented in a separate publication.

Observations O1–O4 can, thus, lead to the hypothesis that the short-range airborne route is predominant, with long-range airborne as its continuation (Figure 1). This hypothesis agrees well with the expired jet dilution theory described above. At least two other phenomena can be predicted from the hypothesis. Infection seems to be minimized when the majority of the public wear a mask, that is, mass masking (P5). Indoor spaces with moderate or vigorous activity and/or loud speaking or singing, such as gyms, choirs,⁷ and meat-processing plants, have shown high infection rates (P6).

One can predict that blockage of the expired jet of an infected individual would significantly minimize, or even eliminate, the short-range airborne route. With the additional filtration effect of masks, for both infected and susceptible individuals, mass masking should successfully inhibit transmission (P5), although leaked aerosols may lead to probable long-range airborne transmission. However, mask wearing by only a small fraction of the population would not be effective, as there is a good chance that some or most individuals were infected because they did not wear a mask. How do we explain the high infection risk in rooms with moderate or vigorous activity and/or loud speaking or singing (P6)? Vigorous activity results in 5–7 times larger exhalation flow rates than the number at rest.¹⁶ Thus, an infected individual engaging in vigorous activity may release 5–7 times more droplets than an infected individual at rest, and a susceptible individual engaging in vigorous activity in the same room may inhale 5–7 times more droplets. Thus, the infection risk in a room with vigorous activity becomes 25–49 times higher than that in a room with individuals at rest or engaged in mild activity. I refer to this as the generation-inhalation double-multiplier effect, which makes inspiratory exposure to respiratory aerosols different from exposure to conventional indoor air pollution, for which only a single inhalation multiplier effect exists. If the minimum ventilation rate is 10 L/s per person in a room with individuals at rest, it becomes 250–490 L/s per person in a room where individuals are engaging in vigorous activity. The current ventilation standards do not fully account for respiratory infection control. The minimum ventilation rate in a room where

individuals engage in vigorous activity, such as a gym, is designed to be much lower than 250–490 L/s per person. The high infection rates seen in spaces where vigorous activity or singing/loud speaking occur are likely to result from insufficient ventilation, leading to long-range airborne transmission. Long-range airborne transmission only occurs when ventilation is insufficient, or the exposure time is significant; hence, long-range airborne transmission is opportunistic.

Note that no statistics related to the observed phenomena are included here. The inherent assumption behind the hypothesis presented here is that SARS-CoV-2 is mainly transmitted by expired virus-containing aerosols. Therefore, other aerosols, such as toilet aerosols, are not expected to play a major role in transmission in the wider community, although they may be important in specific settings. Some more predictions than P5–P6 can be made from the presented hypothesis. First, indoor transmission at typical inter-personal distances (0.7–1 m) is greater in rooms with poor ventilation. Second, in outdoor settings, vigorous activity and loud conversation may lead to infection at close contact. Third, wearing an N95 mask would minimize the risk of healthcare workers being infected by COVID-19 patients, but failure to wear a N95 mask would present a risk. Finally, as expired droplets play a major role in the transmission of SARS-CoV-2, splashing in wash basin sinks also presents a risk. I would encourage the readers to identify other major phenomena of SARS-CoV-2 transmission, or use the theory presented in Figure 1 to predict other trends in the pandemic that we have not identified thus far, to verify or reject our theory.

5 | SUFFICIENT VENTILATION AND ADEQUATE OCCUPANCY SHOULD BE TOP PRIORITIES

Currently, the WHO recognizes the possible role of airborne transmission in the spread of SARS-CoV-2 in special settings, but it has yet to recognize the likely predominance of the short-range airborne route. Thus, the significant adverse effect of poor ventilation (≤ 3 L/s per person) on short-range airborne transmission has also not been recognized. Existing ventilation standards, such as ASHRAE 62.1, do not consider infection control as their objective. There is a need to develop a set of minimum ventilation rates for indoor spaces used for different activities. A home may have adequate ventilation for existing family members, but when relatives or friends visit, the occupancy situation changes and the ventilation may become inadequate. This may explain the significant number of outbreaks observed after family gatherings.¹⁰ Ventilation is not usually considered as a parameter when choosing an indoor space for activities. As discussed earlier, in spaces used for moderate or vigorous activities, existing ventilation standards recommend much lower minimum ventilation rates than those required for infection control, due to the generation-inhalation double-multiplier effect. The predominance of the short-range airborne route of SARS-CoV-2 transmission strongly

suggests the need for healthcare workers who care for COVID-19 patients to wear an N95 mask.

Ventilation rates can be enhanced in some buildings using simple strategies, such as changing fan settings or opening windows, but in many buildings, such improvements are not possible in the short term. In this case, determining the maximum occupancy may be possible by measuring the ventilation rates or using CO₂ monitoring to detect insufficient ventilation rates. However, the CO₂ monitoring method may not work well in situations where exhalation is not the only CO₂ source. Moreover, CO₂ monitoring cannot account for non-ventilation mechanisms for the removal of infectious aerosols, such as virus deactivation, deposition, and filtration. Strong coughing, loud talking, and singing are known to increase virus generation but may not necessarily have the same impact on CO₂ generation. Nevertheless, monitoring ventilation rates using CO₂ warrants further investigation in the near future.

KEYWORDS

COVID-19, long-range airborne transmission, SARS-CoV-2 transmission, short-range airborne transmission, ventilation

ACKNOWLEDGEMENTS

This work was supported by the Hong Kong Research Grants Council via a General Research Fund project (no. 17202719) and a Collaborative Research Fund project (no. C7025-16G).

CONFLICT OF INTEREST

There is no conflict of interest declared.

PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/ina.12837>.

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